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(54) Title: THERAPEUTIC COMPOSITIONS COMPRISING AMINO SULFONIC ACIDS AND THEIR USES

(57) Abstract: The use of at least one zwitterionic amino sulfonic acid, having at least one pKa at 25-38°C in the range of 7.3 ± 0.5, in the preparation of a medicament for the treatment or prevention of photo and non-photoageing of the skin, iatrogenic skin dryness, mucosal membrane dryness (iatrogenic or non-iatrogenic), skin dryness associated with all forms of psoriasis, skin dryness associated with both photo and non-photo ageing of skin, skin dryness in all forms of dermatitis, skin dryness in all forms of eczema, and skin dryness in all forms of ichthyosis, provided that the medicament does not contain urea, is provided. A moisturiser and free radical scavenging and dermal and epidermal cell protective compositions are also provided.

THERAPEUTIC COMPOSITIONS COMPRISING AMINO SULFONIC ACIDS AND THEIR USES

This invention relates to the use of zwitterionic amino sulfonic acids and their derivatives and chemically related molecules in the treatment of skin disorders, non-dermatological inflammatory and other disease conditions.

Dermatological disorders and non-dermatological inflammatory disorders affect significant numbers of the population for a large proportion of their lives. At present, most treatments in the field of dermatology are aimed at providing symptomatic relief only, and this is often at the cost of side effects of varying severity. The current situation can be summarised as follows:

Ichthyosis is a group of often inherited diseases which may be characterised by scaly, dry and often itchy skin. Treatments for genetically and non-genetically linked ichthyoses are different. The principal known treatments which have been used to greater or lesser success are: hydration of the skin with an emollient, which is common to all ichthyoses; in addition, use of a descaling topical salicylic acid product may be indicated in ichthyosis vulgaris, lamellar ichthyosis and sex-linked ichthyosis, all of which are genetically linked; oral retinoids, and in particular isotretinoin may be used as effective treatments for the scaling associated with most ichthyoses, although they may cause dryness of the skin themselves.

It is apparent that there is no simple, cost-effective remedy for conditions such as ichthyosis, which is free of significant, deleterious side effects.

Dermatitis is a general term to denote a group of conditions which may be characterised by superficial skin inflammation presenting with redness, oedema, oozing, crusting scaling and usually itching. Conditions within the grouping include but are not limited to contact dermatitis (caused by a delayed hypersensitivity reaction or direct contact with a skin irritant), atopic dermatitis (also known as atopic eczema, an immune response disease often co-existing with hay fever and/or asthma), seborrheic dermatitis (known as "cradle cap" in infants), chronic dermatitis of hands and feet (in response to mechanical or chemical

trauma), and generalised exfoliative dermatitis (a condition for which often no specific cause is found).

There are various causes of the different dermatitis conditions and treatment will be different for each. In general, treatment is aimed at identifying and resolving or controlling the underlying cause of the dermatitis. However, symptomatic treatment of the dryness and itchiness that often presents may be achieved with topical emollients. There appears to be no simple, widely efficacious, cost-effective remedy for conditions such as dermatitis, which is free of significant, deleterious side effects.

Many drugs may cause dryness of the mucous membranes and skin irrespective of the route of their administration. In many instances, the mechanism of this is not understood. Drugs that have been recorded to cause iatrogenic skin and mucous membrane dryness include, but are not limited to, oral and topical retinoids, omeprazole, buserelin, calcipotriol, fluoxetine, famotidine, ganciclovir, losartan and topical metronidazole.

In most cases, symptomatic treatment with an emollient may be used to counter the skin dryness, although in some cases, cessation of drug treatment is needed. It is already known that the use of urea at low concentrations in topical products for the skin can provide an enhanced moisturising or hydrating effect over that provided by the emollient, occlusive or moisturising topical base itself. This moisturising effect of urea is clearly applicable to most skin conditions where dryness is a feature. This effect is due to the ability of urea to take up and subsequently release water of hydration. Urea suffers from the drawback, however, that it is potentially toxic to the cells of the skin given that it is readily converted, via biuret, to ammonia (Merck Index, 11th Edn). This production of ammonia is due, at least in part, to skin microorganisms. The liberation of ammonia on the skin also makes urea - containing products particularly unpleasant from the point of view of their smell.

Overall, there appears to be no simple, cost-effective remedy for conditions such as iatrogenic skin and mucous membrane dryness, which is free of significant side effects yet has the potential to allow the causatory drug treatment to continue for the benefit of the patient.

So called "normal" ageing of the skin is a common problem which may affect most human beings. It is widely accepted that high levels of exposure to strong sunlight over a prolonged period of time generally accelerates the rate of skin ageing. Therefore, the process of skin ageing can be broken down into photo and non-photo associated components.

Exposure of the skin to UVA in sunlight can lead to an increase in the levels of free radicals in the skin which produce tissue damage in a variety of ways. These may include crosslinking of proteins such as collagen, release of degradative enzymes such as proteases, including elastase, and inhibition of oxidative enzymes in fibroblasts and keratinocytes. At a microscopic level, non-photo associated components of skin ageing may lead to a decrease in the life of fibroblasts, thickening of fibrillar dermal elements, a decrease in hyaluronan concentration with consequent decrease in water levels in the tissues, and a change in the structure and composition of elastins.

Macroscopically, skin ageing resulting from both photo and non-photo causes may be characterised by dryness of the skin, loss of elasticity of the skin, an increase in wrinkles, an increase in susceptibility to topical infections and infestations, and a general deterioration in the quality of the skin.

Many different cosmetic products are available for the prevention and treatment of skin ageing and the signs of skin ageing. Many different approaches have been used with greater or lesser success, including, but not limited to, topical application of known free radical scavengers such as beta-carotene and retinoids, hydrating agents such as simple moisturisers or urea containing products, and collagen containing topical products to replace lost collagen. It is apparent from experience, however, that there is no simple, generally useful, cost-effective remedy for photo and non-photo skin ageing.

Psoriasis is a chronic recurrent disease characterised by dry well circumscribed, silvery scaling papules and plaques of various sizes and skin dryness in affected areas. The severity of the disease can vary from small scaly patches on the elbows and knees to large

plaques and papules covering 40 - 50% of the body. Whilst the exact aetiology of the disease has not yet been fully elucidated, it is believed to involve a large genetic component. It is known that on a cellular level, the plaques are caused by hyperproliferation of undifferentiated keratinocytes. In addition, tissue infiltration by neutrophils and a range of T-cells may be a prominent feature of the disease. At a biochemical level, psoriasis is generally recognised as being an auto-immune disease involving excess production of or presence in the affected tissues of oxygen free radicals, interleukin 1 (IL-1), leukotriene B₄ (LTB₄), and tumour necrosis factor (TNF). The most common kind of psoriasis is psoriasis vulgaris, however, a rarer kind known as pustular psoriasis in which sterile pustules occur on the palms and soles also occurs. Due to the immune system involvement in both of these kinds of psoriasis, psoriatic arthritis may develop in a low percentage of patients as a side effect of the disease.

To date, as with all other auto-immune diseases, methods of treatment have only been able to control the disease rather than providing a final cure. The principal known treatments which have been used with greater or lesser success include:

- 1) Topical corticosteroids, which may be used as treatments for acute disease flare ups. Corticosteroids enter the cytosol of keratinocytes and alter DNA synthesis and hence rate of maturation of the cell. Corticosteroids also possess anti-LTB4 and anti-oxygen free radical actions. Toxicity of corticosteroids increases with potency, and may include disease rebound or relapse upon withdrawal, cutaneous atrophy, epidermal stretching and pituitary-adrenal-axis suppression;
- 2) Topical preparations of coal tar which suppresses epidermal DNA synthesis, and hence plaque formation, may be used for day to day treatment of mild to moderate psoriasis. Side effects of coal tar include skin irritation and acne like eruptions. Furthermore, use is limited by the unpleasant smell of coal tar preparations and their ability to stain skin and clothing. In addition, use of these products may be compromised due to the carcinogenic nature of coal tar;

- 3) Topical salicylic acid, which may be used in psoriasis to enhance the rate of scale loss. The major side effect of such preparations, however, may be skin irritation itself;
- 4) Topically applied dithranol preparations, which have been used effectively for moderate to severe psoriasis. However, they may often cause intense skin irritation and burning;
- 5) Topical vitamin D analogs such as calcipotriol and tacalcitol, which interfere with keratinocyte proliferation and enhance proper keratinocyte differentiation. These topical products may be used for treating mild to moderate psoriasis. However, recorded side effects include skin dryness, local irritation, photosensitivity and hypercalcaemia;
- 6) Oral retinoids, including etretinate and it's active metabolite acitretin, which counter the hyper-proliferation and lack of differentiation of keratinocytes in psoriasis. They also have anti-inflammatory effects in their own right. Due to their side effects, which may include dryness of mucous membranes, thinning of the skin, photosensitivity, skeletal hyperostosis, myalgia and arthralgia, these drugs have been reserved for severe extensive psoriasis resistant to other treatments;
- 7) Cyclosporin, which has anti-T cell properties, may be used in severe or recalcitrant psoriasis. Its restriction to severe disease is due to its side effects which can include hypertension, gingival hypertrophy, hepatic and renal impairment and neuropathy;
- 8) Methotrexate, a dihydrofolate reductase inhibitor and consequently an anti-metabolite may also be used in the treatment of severe psoriasis. Side effects can include bone marrow suppression, hepatic and renal damage, skin reactions and teratogenesis; and
- 9) Combination treatments using UVA and UVB with dithranol or light sensitising psoralens such as 5-methoxysoralen, which have been used successfully in moderate to severe psoriasis. Due to their complicated nature, these treatment regimens have only been used in clinic settings and are therefore extremely expensive.

It is apparent, therefore, that there is no simple, widely applicable, cost-effective remedy for conditions such as psoriasis, which is free of significant, deleterious side effects.

Non-dermatological inflammatory diseases include, but are by no means limited to:

A) Inflammatory bowel disease: a group of inflammatory bowel disorders with overlapping clinical, epidemiological and pathological findings, but without a definite aetiology and including both ulcerative colitis and Crohn's disease. Whilst both diseases can be characterised by chronic non-specific inflammation of the gastrointestinal tract, ulcerative colitis is limited to the colonic mucosa, whereas Crohn's disease can effect any part of the GI tract from the mouth to the anal and perianal regions. In addition, unlike Crohn's disease, ulcerative colitis is also characterised by ulceration and bleeding in the colon, consequently presenting with bloody diarrhoea. Both diseases present with abdominal discomfort, weight loss and diarrhoea. As with psoriasis, the underlying aetiology of both diseases is not yet fully understood, but genetic, infectious and vascular factors as well as the composition of the protective mucous layer are all thought to be important. On the cellular level, amongst other things both diseases present with raised T-cell and neutrophil tissue infiltration. On the biochemical level, raised levels of platelet aggregation factor (PAF), LTB₄, IL-1, IL-6 and IL-8, TNF, elastase, collagenase, gelatinase and oxygen free radicals may characterise the diseases.

The treatment regimens for ulcerative colitis and Crohn's disease are broadly similar. 5-aminosalicylic acid containing drugs such as sulphasalazine, mesalazine and olsalazine may be used as the mainstays of long term treatment for both ulcerative colitis and Crohn's disease. The mechanisms of 5-aminosalicylic acid containing drugs have not been fully elucidated, but are thought to include inhibitory or down-regulating effects on LTB₄, oxygen radicals, 5-lipoxygenase (the enzyme that produces leukotrienes) PAF and IL-1. Side effects of this class of drugs may include nausea, vomiting, abdominal discomfort, headache and skin rashes. Orally or rectally administered corticosteroids may be used as therapy in acute flare ups of disease. Due to their side effect profile as outlined previously, their long term use may be contra-indicated. Immunosuppressive treatment with

azathioprine may be used quite commonly in both ulcerative colitis and Crohn's disease. Its side effect profile may include pancreatitis, bone marrow suppression and hepatitis. Unlike azathioprine, cyclosporin is only of clinical value in Crohn's disease, not in ulcerative colitis. Methotrexate may be considered as an alternative to azathioprine or cyclosporin in patients with intolerable side effects to these agents. However, methotrexate itself has a large side effect profile, as outlined above. Metronidazole treatment has been shown to be useful in some Crohn's disease patients with colitis resistant to standard therapy. In this setting, the mechanism of metronidazole has not yet been established. Side effects may include nausea, vomiting, GI disturbances, skin rashes, angioedema and dizziness.

B) Rheumatoid arthritis: and juvenile rheumatoid arthritis are chronic syndromes of the peripheral joints which may be characterised by non-specific, usually symmetrical inflammation of the joints, normally leading to progressive destruction and deformation of articular and peri-articular structures. Generalised systemic manifestations may also present. As with many other complex diseases, the exact aetiology is not yet fully understood, but is thought to have genetic, auto-immune and infectious components. Patients may initially present with inflammation of the joint with progressive loss of joint function, eventually leading to fusing of the joint and complete loss of joint function. The disease is characterised by raised levels of LTB₄, neutrophils, oxygen free radicals, IL-1, TNF, T-cells, hyperactivity of metalloproteinases, gelatinases and collagenases and the presence of Rheumatoid Factor (RF).

Drug treatment of rheumatoid arthritis may be divided between non-steroidal anti-inflammatory drugs (NSAIDs) which may be used for pain control and control of inflammation, and slow acting disease modifying drugs designed to affect the progression of the actual disease. The principal known treatments which have been used with greater or lesser success include:

NSAIDs, which may be used for treatment, are a chemically disparate group of drugs with a common mechanism of action. All members of the group may exert their analgesic and anti-inflammatory actions by inhibiting cyclo-oxygenase-2 (COX-2) thereby preventing the production of pro-inflammatory prostaglandins. Whilst inhibition of COX-2 is desirable, to

date all NSAIDs also inhibit COX-1 to a greater or lesser degree, which may lead to loss of cytoprotective prostaglandin E₁ and GI bleeding and potential ulceration as major side effects.

5-aminosalicylic acid containing drugs such as sulphasalazine, olsalazine and mesalazine, as well as corticosteroids and methotrexate may all be used to slow or halt the progression of rheumatoid arthritis. Their mechanisms and possible side effects are outlined above.

The exact mechanism of action of gold salts such as sodium aurothiomalate and auranofin, which may be used to slow or halt the progression of the disease is not known, but they are believed to decrease IL-1 production, scavenge oxygen radicals and possibly have anti-LTB4 actions. Side effects can include dermatitis, inflammation of the mucous membranes, various blood dyscrasias and hepatitis.

As with gold salts, the exact mechanism of action of D-penicillamine, which may be used for treatment, is unknown, however, free radical scavenging, anti-T cell and modification of collagen formation effects have been shown. Whilst up to 75% of patients respond to penicillamine, a high proportion (up to 40%) of those suffer side effects that necessitate cessation of treatment. These can include myasthenia gravis, thrombocytopenia, rashes and aphthous ulcers.

Chloroquine and hydroxychloroquine, which may be used for treatment, appear to have various mechanisms of action including inhibition of phospholipase A2 (therefore decreasing levels of leukotriene and PAF) interference with hydrolase activity, free radical scavenging, decrease of IL-1 production and inhibition of leukocyte chemotaxis. Side effects of long term use of these drugs can include haemolytic anaemia, rashes, ototoxicity and rarely retinopathy.

C) Asthma: a lung disease which may be characterised by reversible bronchoconstriction, inflammation of the pulmonary tissues and an increased airway responsiveness to a variety of stimuli, particularly allergens. The exact underlying cause of the disease is not fully understood. However, the disease presents with increased mast cell

release of histamine granules, neutrophil and eosinophil infiltration of the tissues, raised levels of LTB₄ and LTC₄D₄ and E₄ (known as the Slow Reacting Substance of Anaphylaxis (SRSA)) and a raised pulmonary immunogenic response. The importance of LTC₄D₄ and E₄ in the disease has increasingly become recognised, as have the roles of certain phosphodiesterases.

The goal of asthma treatment is to prevent the onset of an acute bronchoconstrictive episode, and then treat the episode should it occur. The principal known treatments which have been used include:

Inhaled corticosteroids, particularly beclomethasone, fluticasone and budesonide, which may be used prophylactically to prevent tissue inflammation. Oral corticosteroids, particularly prednisone and prednisolone may also be used to reduce inflammation in acute asthma attacks requiring hospitalisation. Whilst the side effect profile of inhaled steroids may be significantly lower than in other forms of administration, the use of high doses has raised concerns about adreno-cortical suppression and growth retardation in young children.

Xanthines which include theophylline and aminophylline are bronchodilating agents which may be used prophylactically to maintain bronchoconstriction at a minimum. Their mechanism of action is not clearly understood, although anti-LTB₄ activity is thought to play a significant role. Side effects may include tachycardia, arrhythmias, palpitations and GI disturbances. The risk of side effects may also be enhanced as a result of the very narrow therapeutic window of the xanthines.

Nedocromil and sodium cromoglycate are mast cell stabilisers that prevent the release of bronchoconstrictive histamine from mast cells, and may be used for treatment. These agents, which are of no value in an acute attack, may be used prophylactically. Side effects of these drugs are normally minor and transient.

The anti-histamine ketotifen may be of some use prophylactically in paediatric asthma, although its clinical usefulness in adult asthma may be limited. Its main side effect may be sedation.

Beta-₂ adrenoceptor agonists such as salbutamol, terbutaline and salmeterol appear to reverse the bronchoconstriction during acute bronchoconstrictive episodes by direct stimulation of beta-₂ adrenoceptors in the lung tissue. Their anti-asthmatic action may also in part be mediated by their free radical scavenging effects. Side effects may include tachycardia, fine tremor of the hands and headache. Most of these side effects are often short-lived if the drug is inhaled.

Ipratropium bromide is an inhaled anti-muscarinic agent which may be used for treating bronchoconstriction in an acute asthma attack in patients whose disease is largely mediated by irritant stimuli. As there is no significant systemic absorption from an inhaled dose, there are few reported significant systemic anti-muscarinic side effects.

LTC₄D₄E₄ receptor antagonists such as zafirlukast and montelukast have recently been introduced as adjunct therapies for asthma. Side effects are generally minor but may include headache, skin rashes, abdominal pain, dizziness, insomnia and gastrointestinal disturbances.

D) Chronic Obstructive Pulmonary Disease: a broad term which may be used to describe both chronic bronchitis and emphysema either alone or when presenting concurrently in a patient. In chronic bronchitis, there is a chronic narrowing of the bronchial tract, whereas in emphysema there is a loss of elasticity of the lung tissue. Due to the serious damage to the lung tissue, respiratory tract infections may be common in chronic obstructive pulmonary disease patients.

Therapy is only aimed at relieving the symptoms as tissue damage in both chronic bronchitis and emphysema appears to be irreversible. The principal known treatments which have been used include:

Xanthines, which may be used to minimise bronchoconstriction, whereas beta₂-adrenoceptor agonists may be used for bronchodilation in severe acute cases of dyspnoea.

Corticosteroids are of no value in treating chronic obstructive pulmonary disease with a predominantly emphysemic character, however, they may be of some use in chronic bronchitic chronic obstructive pulmonary disease or chronic obstructive pulmonary disease with co-existing asthma.

E) Gastroduodenal inflammation and ulceration: may be caused by many different factors including the use of NSAIDs and the presence of GI Helicobacter pylori infection. Whilst the exact mechanism of GI inflammation and ulceration is not completely understood, it is believed that NSAID associated gastric ulceration is a neutrophil dependent process, possibly mediated by LTB4 (Wallace JL *et al, Am. J. Physiol.* **259** (3 pt 1) : G462-467, 1990 Sept.). It is also believed that the presence of free radicals is involved in GI tissue inflammation and ulceration in all forms of gastroduodenal inflammation and ulcerations.

Specific treatment for the inflammation and ulceration will be dependent on the underlying cause of the disease. The principal known treatments include:

Antacids, such as magnesium tricilicate and aluminium hydroxide, which may be used to counter excess acid levels. Side effects may include constipation (aluminium products) and diarrhoea (magnesium products).

H₂ receptor antagonists such as ranitidine, famotidine and cimetidine, which may be used to decrease gastric acid production. Whilst significant side effects are rare, inhibition of cytochrome P450 enzyme particularly by cimetidine may be highly problematic when co-administered with drugs metabolised by that enzyme system.

Proton pump inhibitors such as omeprazole, lansoprazole and pantoprazole, which are used to decrease gastric acid production by the parietal cell. Side effects may include dry skin and membranous membranes, diarrhoea and dizziness.

Combinations of antibiotics such as metronidazole, amoxicillin, clarithromycin and tetracycline, used to eradicate Helicobacter pylori infections. Side effects vary according to the antibiotics used and may include diarrhoea, rashes, urticaria, dizziness and darkening of the urine.

Bismuth chelates such as tripotassium dicitratabismuth, which help eradicate Helicobacter pylori. In addition, bismuth chelates are thought to have stimulating effects on the production of cytoprotective mucosal PGE₁. Side effects may include darkening of the tongue and blackening of the faeces.

Sucralfate, believed to form a protective coating over the area of mucosal damage protecting it from gastric acid attack and therefore used to allow recovery of damaged gastric mucosa. Side effects may include constipation, diarrhoea, dry mouth, rash and back pain.

PGE₁ analogs such as misoprostol, which may be used to counter the decrease in cytoprotective PGE₁ caused by the inhibition of COX-1 by most currently used NSAIDs. Side effects may include diarrhoea, abnormal vaginal bleeding, rashes and dizziness.

Zwitterionic amino sulfonic acids have been suggested to have therapeutic potential in certain diseases. In WO97/29745 (Theodore), such compounds are described as biological response modifiers, and it is suggested that they may possess beneficial properties in the treatment of cancer and associated pain, and rheumatoid arthritis. The amino sulfonic acids were administered parenterally in combination with other components selected from vitamins, amino acids and cell culture supernatants.

An early use of the amino sulfonic acids is that described in US4,473,569 and EP0080172A (O'Sullivan). Here it is shown that such compounds, when selected to have a pKa of 6.0 to 8.3 and when applied to the skin in a barrier cream, are able to prevent occurrence of accidental skin adhesion events in people handling cyanoacrylate adhesives. A similar use is reported in IL68768. Furthermore, in IE54490 and EP00827A (O'Sullivan *et al*), the use of compositions containing amino sulfonic acids in the treatment of psoriasis

is proposed, along with a mechanism of action based on suppression of neutrophils. Again, a preference for a pKa of 6.0 to 8.3 is made.

EP0228239A describes the use of topical formulations of selected amino sulfonic acids for the treatment of arthritis and rheumatism. In WO99/27791, compositions for treatment of inflammatory conditions are described, the compositions containing fatty acid esters of amino sulfonic acids having a pKa of 6.0 to 8.3 and intended for use on the skin.

In US5,248,680 (Bloomfield) and EP0469813A, the treatment of chronic, progressive inflammatory conditions using zwitterionic amino sulfonic acids and their N-halo derivatives is proposed. Whilst this document shows some effect of the amino sulfonic acids on immune cell and enzyme function, the experiments concentrating on the activity of the enzyme myeloperoxidase, it does not reveal any clear evidence of a general usefulness of the compounds in the field of dermatology. Furthermore, the experiments discussed in this document are apparently not performed at physiological pH or pHs within the buffering range of HEPES (N-[2-hydroxyethyl]piperazine-N'-[2-ethanesulfonic acid]), the compound used for most of the experiments.

WO96/23490 discloses compositions for inhibiting skin irritation, the compositions containing multiply-protonated organic polyamines. HEPES is used as an example of a heterocyclic polyamine. In EP1090630A, skin conditioners suitable for treatment of atopic dermatitis and for skin moisture retention are presented. Preferred active ingredients are L-arginine and ethanolamine.

In EP 0993825A, compositions for the moisturisation and protection of human skin are shown, the compositions containing, as an essential moisturising ingredient, urea. N-substituted amino sulfonic acids are added solely in an attempt to slow the degradation of the urea.

None of these prior art documents identifies means by which zwitterionic amino sulfonic acids can be generally applied to the treatment of conditions dependent upon or susceptible

to the interconversion of reactive oxygen species, nor do they provide guidance as to the use of zwitterionic amino sulfonic acids *per se* as moisturising agents.

It is an object of the present invention to provide therapeutically and cosmetically acceptable compositions and methods for treating abnormal dermatological disorders and non-dermatological inflammatory conditions.

Accordingly, one aspect of the present invention provides the use of at least one zwitterionic amino sulfonic acid, having at least one pKa at 25-38°C in the range of 7.3 ± 0.5 , in the preparation of a medicament for enhancement of superoxide dismutase activity.

In another aspect, the invention provides a method of enhancing the activity of superoxide dismutase in a patient, the method comprising administering to a patient in need of such treatment an effective superoxide dismutase activity enhancing amount of a composition comprising at least one zwitterionic amino sulfonic acid having at least one pKa at 25-38°C in the range of 7.3 ± 0.5 .

A further aspect of the invention provides a moisturiser comprising at least one zwitterionic amino sulfonic acid having at least one pKa in the range 7.3 ± 0.5 at 25-38°C, the moisturiser not containing urea. The moisturiser of this invention may also include one or more other active ingredients known to be efficacious in the treatment or prevention of photo and non-photoageing of the skin, iatrogenic skin dryness, mucosal membrane dryness (iatrogenic or non-iatrogenic), skin dryness associated with all forms of psoriasis, skin dryness associated with both photo and non-photo ageing of skin, skin dryness in all forms of dermatitis, skin dryness in all forms of eczema, and skin dryness in all forms of ichthyosis. Inert, pharmaceutically acceptable excipients may also be included.

Compositions in accordance with the invention are particularly useful for treating or preventing photo and non-photoageing of the skin, iatrogenic skin dryness, mucosal membrane dryness (iatrogenic or non-iatrogenic), skin dryness associated with all forms of psoriasis, skin dryness associated with both photo and non-photo ageing of skin, skin

dryness in all forms of dermatitis, skin dryness in all forms of eczema, and skin dryness in all forms of ichthyosis.

In another aspect, the invention provides the use of at least one zwitterionic amino sulfonic acid, having at least one pKa at 25-38°C in the range 7.3 ± 0.5 , in the preparation of a medicament for moisturisation of the skin and/or mucosal membranes, provided that the medicament does not contain urea.

In a further aspect, the invention provides a pharmaceutical composition comprising at least one zwitterionic amino sulfonic acid having at least one pKa at 25-38°C in the range 7.3 ± 0.5 , in combination with one or more agents of known efficacy in the prevention or treatment of the abnormal dermatological disorders and/or non-dermatological inflammatory conditions described in this document, for use in therapy by co-administration or by sequential administration, the composition not containing urea.

The invention also provides, in yet another aspect, the use of at least one zwitterionic amino sulfonic acid, having at least one pKa at 25-38°C in the range 7.3 ± 0.5 , and at least one other compound known to be efficacious in the treatment or prevention of dermatological disorders and/or non-dermatological inflammatory conditions in the preparation of a medicament for the treatment of dermatological disorders and/or non-dermatological inflammatory conditions by co-administration or by sequential administration, provided that the medicament does not contain urea.

In yet another aspect, the invention provides the use of at least one zwitterionic amino sulfonic acid, having at least one pKa at 25-38°C in the range 7.3 ± 0.5 , in the preparation of a medicament for the treatment or prevention of photo and non-photoageing of the skin, iatrogenic skin dryness, mucosal membrane dryness (iatrogenic or non-iatrogenic), skin dryness associated with all forms of psoriasis, skin dryness associated with both photo and non-photo ageing of skin, skin dryness in all forms of dermatitis, skin dryness in all forms of eczema, and skin dryness in all forms of ichthyosis, provided that the medicament does not contain urea. The selected pKa range for the amino sulfonic acids helps to ensure minimal adverse effects on the surface to be treated or in any other body system by

maintaining a pH as close as possible to that of the non-diseased surface or non-diseased body system. The medicament may include, or may be administered in addition to as part of a treatment regimen, other active compounds known to be of use in the conditions.

In yet another aspect, the invention provides a method of cosmetically improving the appearance of the skin, the method comprising the application to the skin of a composition comprising, as an active ingredient, at least one zwitterionic amino sulfonic acid having at least one pKa at 25-38°C in the range 7.3 ± 0.5 provided that the composition does not contain urea. Optionally, the cosmetic composition may also include one or more agents known to be efficacious in the treatment or prevention of photo and non-photoageing of the skin, any form of ichthyosis, any form of dermatitis, any form of psoriasis, iatrogenic skin dryness, mucosal membrane dryness (iatrogenic or non-iatrogenic), skin dryness associated with all forms of psoriasis, skin dryness associated with both photo and non-photo ageing of skin, skin dryness in all forms of dermatitis, skin dryness in all forms of eczema, and skin dryness in all forms of ichthyosis.

Another aspect of the invention provides a hydroperoxyl radical and/or hydrogen peroxide scavenging composition comprising at least one zwitterionic amino sulfonic acid having at least one pKa at 25-38°C in the range 7.3 ± 0.5 . The invention also provides the use of at least one zwitterionic amino sulfonic acid having at least one pKa at 25-38°C in the range 7.3 ± 0.5 in the preparation of a medicament for scavenging hydroperoxyl radicals and/or hydrogen peroxide. The hydroperoxyl radicals and/or hydrogen peroxide may be extracellular.

The invention also provides, in yet another aspect, a method of scavenging hydroperoxyl radicals and/or hydrogen peroxide, the method comprising administering to a patient in need of such treatment an effective scavenging amount of a composition comprising at least one zwitterionic amino sulfonic acid having at least one pKa at 25-38°C in the range 7.3 ± 0.5 .

Yet a further aspect of the present invention provides the use of at least one zwitterionic amino sulfonic acid having at least one pKa at 25-38°C in the range 7.3 ± 0.5 in the

preparation of a medicament for improving epidermal cell integrity and normalising dermal survival, growth, maturation and replication.

The invention also provides, in yet another aspect, a dermal and epidermal cell survival enhancing composition comprising at least one zwitterionic amino sulfonic acid having at least one pKa at 25-38°C in the range 7.3 ± 0.5 . In a further aspect, the invention provides the use of at least one zwitterionic amino sulfonic acid having at least one pKa at 25-38°C in the range 7.3 ± 0.5 in the preparation of a medicament for improving epidermal cell integrity and normalising dermal survival, growth, maturation and replication. Another aspect of the invention provides a method of improving epidermal cell integrity and normalising dermal survival, growth, maturation and replication, the method comprising administering to a patient in need of such improvement and normalisation an effective normalising amount of a composition comprising at least one zwitterionic amino sulfonic acid having at least one pKa at 25-38°C in the range 7.3 ± 0.5 .

In yet a further aspect, the invention provides a method of treatment or prevention of photo and non-photoageing of the skin, skin dryness associated with photo and non-photo ageing of skin, skin dryness associated with all forms of psoriasis, iatrogenic skin dryness, mucosal membrane dryness (iatrogenic or non-iatrogenic), skin dryness in all forms of dermatitis, skin dryness in all forms of eczema and skin dryness in all forms of ichthyosis, the method comprising the administration of a therapeutically effective amount of at least one zwitterionic amino sulfonic acid having at least one pKa at 25-38°C in the range 7.3 ± 0.5 to a patient in need of such treatment, provided that the treatment does not also include the administration of urea. Optionally, the method may also include the administration of one or more agents (either together with the amino sulfonic acid in a single pharmaceutical or cosmetic form, or sequentially in individual pharmaceutical or cosmetic forms) used for the prevention or treatment of the said abnormal conditions.

A further aspect of the invention provides a method of moisturisation of the skin or mucosal membranes, the method comprising administering to a patient in need of such moisturisation an effective moisturising amount of a composition comprising at least one

zwitterionic amino sulfonic acid having at least one pKa at 25-38°C in the range 7.3 ± 0.5, provided that the composition does not contain urea.

Preferred zwitterionic amino sulfonic acids for the purposes of the present invention are:

ACES (N-[Carbamoylmethyl]-2-aminoethanesulfonic acid), free acid and all metal salts (pKa=6.8 at 25°C);

PIPES (Piperazine-N,N'-bis[2-ethanesulfonic acid]), free acid and all metal salts (pKa=6.8 at 25°C);

MOPSO (3-[N-morpholino]-2-hydroxypropanesulfonic acid), free acid and all metal salts (pKa=6.9 at 25°C);

BIS-TRIS-Propane (1,3-bis[tris(hydroxymethyl)methylamino]propane), free base and all salts (pKa=6.8 at 25°C);

BES (N,N-bis[2-hydroxyethyl]-2-aminoethanesulfonic acid), free acid and all metal salts (pKa=7.1 at 25°C);

MOPS (3-[N-morpholino]propanesulfonic acid), free acid and all metal salts (pKa=7.2 at 25°C);

TES (N-tris[hydroxymethyl]methyl-2-aminoethanesulfonic acid), free acid and all metal salts (pKa=7.4 at 25°C);

HEPES (N-[2-Hydroxyethyl]piperazine-N'-[2-ethanesulfonic acid]), free acid and all metal salts (pKa=7.5 at 25°C);

DIPSO (3-[N,N-bis(2-hydroxyethyl)amino-2-hydroxy-propanesulfonic acid), free acid and all metal salts (pKa=7.6 at 25°C);

MOBS (4-[N-morpholino]butanesulfonic acid), free acid and all metal salts (pKa=7.6 at 25°C);

TAPSO (3-[N-tris(hydroxymethyl)methylamino]-2-hydroxypropanesulfonic acid), free acid and all metal salts (pKa=7.6 at 25°C);

HEPPSO (N-[2-hydroxyethyl]piperazine-N'-[2-hydroxypropanesulfonic acid), free acid and all metal salts (pKa=7.8 at 25°C); and

POPSO (Piperazine-N,N'-bis[2-hydroxypropanesulfonic acid), free acid and all metal salts (pKa=7.8 at 25°C).

Preferably, one of the zwitterionic amino sulfonic acids used in the compositions or methods according to the present invention is HEPES.

The compositions according to the present invention preferably include one or more excipients appropriate to the type of formulation, as would be obvious to those skilled in the art. Different routes of administration for such formulations include, but are not limited to, topical, oral, buccal, rectal, parenteral or pulmonary routes.

For use in skin disorders, the compositions are preferably administered topically.

In the case of those compositions of the present invention which do not contain urea, the presence of urea or its derivatives is at or below a level which does not lead to any physiological effects, such that the invention is intended to extend to compositions containing merely a colourable amount of urea or a derivative thereof, such as might result from an impurity or from the addition of an incidental or ineffectual amount.

The invention will now be described in more detail by way of example only. Reference is made to the appended drawing, which shows the results of an experiment looking at the effect of pH on superoxide dismutase activity.

A) CompositionsExample 1

A cream for topical administration is made up from the following recipe:

Oily phase

Material	% W/W
Low melting point microcrystalline wax	3
Sunflower oil	4
Tween 20	12
Glycerol monostearate	3
Stearic acid	6
Coconut oil	1.5

Aqueous phase

HEPES	1.5
Water	to 100

The ingredients in the oily phase are melted together and brought to 75 °C. The ingredients of the aqueous phase are mixed together until the HEPES is dissolved in the water and brought to 75 °C.

The oily phase is added to the heated aqueous phase and the two phases thoroughly mixed. The emulsified mixture is allowed to cool to about 40 °C (whilst continually stirring the mixture) at which point the mixture is packed in a suitable container so as to prevent water loss.

Example 2

A composition for a capsule for oral administration is made up from the following recipe:

Material	Weight per capsule (mg)
HEPES	50.0
Silicone dioxide	3.5
Magnesium stearate	0.5
Maize starch	296.0

The components are thoroughly mixed using appropriate equipment e.g. a Y-blender and then filled into hard gelatine capsules using a capsule filler.

The capsules are then coated with a pH control enteric coat e.g. Eudragit to ensure release of the active at the required place and time in the gastrointestinal tract.

For co-administration with an agent of known efficacy in the treatment of dermatological disorders or non-dermatological inflammatory conditions, a suitable amount of the agent of known efficacy is incorporated into the capsule powder mixture and the starch content is reduced accordingly. For sequential administration, separate dosage forms containing the agent of known efficacy are prepared and presented alongside the HEPES capsules, together with instructions as to dosage and use.

B) Moisturisation

Example 3

Loss of water from skin tissue is caused by a variety of different mechanisms, such as those at work in photo and non-photo ageing of skin, psoriasis and iatrogenic skin dryness, which are understood, whilst others such as in ichthyosis or atopic dermatitis are less well understood. However, the resulting symptom of dry and often itchy skin is the same irrespective of the underlying mechanism.

The use of molecules such as urea as humectants for the rehydration of skin in dry skin conditions such as psoriasis is well established. Like urea, the zwitterionic amino sulfonic acids described above are heavily hydrated and able to give up their water of hydration at or around physiological pH. HEPES has a solubility of around 3.47M (free acid) and 3.33M (sodium salt) at 33°C. This compares favourably with urea which has

a solubility of around 5M.

The zwitterionic amino sulfonic acids can therefore act as water carriage and delivery molecules. The zwitterionic amino sulfonic acids of this invention are therapeutically and cosmetically efficacious in rehydration of skin and mucosal surfaces. Unlike urea, however, they do not liberate toxic ammonia or biuret on the skin or mucosal surface. This feature makes the compositions of the invention safer and more pleasant to use, as well as being less prone to degradation on storage.

C) Antiinflammatory Enzyme Enhancement

Example 4

A range of inflammatory diseases including psoriasis, ulcerative colitis, Crohn's disease and rheumatoid arthritis are characterised by, amongst other things, infiltration into the inflamed tissues of neutrophils, with a consequent increase in the local levels of reactive oxygen species, degradative enzymes and LTB₄, all of which are produced by the neutrophils. Reactive oxygen species and degradative enzymes all contribute to tissue damage in the inflammatory tissues. LTB₄ (a derivative of cell membrane associated arachidonic acid), which is the most potent chemotactic agent known in the body, powerfully attracts more neutrophils to the site of inflammation and activates them to produce more reactive oxygen species and LTB₄ and to release more degradative enzymes. Via this mechanism, an ongoing cycle of LTB₄ production and neutrophil attraction and activation is set up. This cycle is responsible to a greater or lesser extent for the perpetuation, progression and initiation of the inflammatory diseases listed above. Many pharmaceutical and biotechnology research companies are currently evaluating LTB₄ receptor blockers or LTB₄ synthesis inhibitors for use in inflammatory diseases.

In asthma and chronic obstructive pulmonary disease, whilst there is an increase in neutrophil and eosinophil tissue infiltration and LTB₄ levels, LTB₄ is not as important in the pathogenesis of the disease as the cysteinyl leukotrienes LTC₄D₄E₄ (SRSA). These molecules are also derived from cell membrane associated arachadonic acid. Experiments have shown that raised levels of LTC₄D₄ and E₄ in asthma patients are

partially or fully responsible for the bronchoconstriction, increase in mucus secretion and increase in vascular permeability seen in the disease, and within the past few years, two LTC₄D₄E₄ receptor antagonists, zafirlukast (UK Product Licence No 12619/0108) and montelukast (UK Product Licence Nos 0025/0357 and 0025/0358) have been registered and launched for the treatment of asthma. In addition, a range of 5-lipoxygenase inhibitors are currently under investigation for the treatment of asthma.

In addition, it has been discovered that some of the drugs currently used to treat inflammatory diseases of membranous surfaces such as ulcerative colitis, Crohn's disease, rheumatoid arthritis and asthma exert some of their action via anti-leukotriene mechanisms. Drugs whose mechanism in inflammatory diseases are thought to be at least partly mediated by anti-leukotriene mechanisms include corticosteroids, such as hydrocortisone, betamethasone and prednisolone, beta-₂ adrenoceptor agonists, such as salbutamol, terbutaline and salmeterol, xanthines, such as theophylline and aminophylline, and nedocromil sodium.

The compositions and uses of the zwitterionic amino sulfonic acids described herein, particularly those employing HEPES free acid and the metal salts of HEPES, maintain the correct pH environment for the supply of ample substrate to neutrophil myeloperoxidase and eosinophil peroxidase. These enzymes form the central part of the myeloperoxidase-hydrogen peroxide-halide and peroxidase-hydrogen peroxide-halide systems which produce hypochlorous acid (HOCl) using hydrogen peroxide and chlorine as substrates. Hypochlorous acid degrades LTB₄ (unpublished laboratory data, and Bloomfield DA and Frederick J US Patent 5248680), LTC₄, LTD₄ and LTE₄ to inactive metabolites (Henderson WR *et al*, *J. Immunol.* **126**(6) : 2609-2613, 1982 and Lee CW *et al*, *J. Biol. Chem.* **258**(24) : 15004-1510, 1983).

Laboratory experiments using neutrophils from psoriasis patients incubated with 10mM HEPES showed a significant decrease in LTB₄ levels (compared to non-incubated neutrophil populations). These laboratory results have been borne out in clinical results using a topical 1.5% HEPES cream for patients with bilateral plaque psoriasis. The disease responded well to this mode of treatment with a decrease in severity of, or even

complete clearing of, plaques and skin inflammation together with an objective and subjective improvement in skin quality. Further clinical results are given in Example 10.

The zwitterionic sulfonic acids described herein, particularly those employing HEPES free acid and the metal salts of HEPES, crucially maintain the correct pH environment to optimise the activity of superoxide dismutase (SOD) to create H₂O₂ as a substrate for the myeloperoxidase-hydrogen peroxide-halide and peroxidase-hydrogen peroxide-halide systems. In the appended drawing, SOD is demonstrated not to be active at acidic pHs, that is, pH below 6.0 to 6.5 (for further details of the SOD assay, see Example 5).

The zwitterionic amino sulfonic acids used according to this invention have therapeutic efficacy either alone or in combination with other agents (either administered together in a single pharmaceutical or cosmetic form, or sequentially in individual pharmaceutical or cosmetic forms) such as, but not limited to, those used conventionally in the treatment of the dermatological conditions described herein.

D) Free Radical Scavenging

Example 5

The production and presence of free radical molecules of any kind, particularly reactive oxygen species, at and around a site of inflammation are well accepted to significantly contribute to tissue damage and perpetuation of inflammation in a number of mammalian inflammatory diseases of membranous surfaces, including the conditions already described. Free radicals in general are known to be a significant cause of the degenerative changes associated with both photo and non-photoageing of mammalian skin.

The use of free radical scavengers and anti-oxidants such as alpha-tocopherol and ascorbic acid in cosmetic "anti-skin ageing" preparations is well established, and their efficacy in helping to slow the "signs of ageing" is now generally recognised. In addition, drugs whose mechanism of action in inflammatory diseases is now thought to

be partly or largely mediated by anti-oxidant or free radical scavenging actions include sulphasalazine, 5-amino salicylic acid, methotrexate, gold salts, corticosteroids, some non-steroidal anti-inflammatory drugs, chloroquine, D-penicillamine, beta₂-adrenoceptor agonists such as salbutamol and ipratropium.

HEPES is known to have antioxidant activity. All other amino sulfonic acids suitable for the present invention contain a piperazine or other moiety susceptible to attack by certain free radicals. It has been found that these compounds are themselves free radical scavengers. As such, they are of use in the treatment of the conditions described, either alone or in combination with other free radical scavenging agents (either administered together in a single pharmaceutical or cosmetic form, or sequentially in individual pharmaceutical or cosmetic forms). Compositions comprising these compounds also have cosmetic efficacy in helping to prevent free radical tissue damage in photo and non-photoageing of skin.

A superoxide dismutase (SOD) assay was performed in 50mM potassium phosphate buffer. Horse heart ferricytochrome C (12.5 µM) and xanthine (50 µM) were mixed with EDTA (100 µM). Sufficient butter milk xanthine oxidase (around 8 nM) was added to give a rate of increase in absorbance of 0.05-0.1 optical density units (550nm) per minute at 30°C (due to xanthine oxidation/cytochrome C reduction). Sufficient SOD was then added to cause inhibition in the rate of the redox reaction by 25-75%. One unit of SOD is defined as that amount of enzyme required to inhibit the above redox reaction by 50%.

With reference to the drawing, it can be seen that superoxide dismutase (SOD), the enzyme primarily responsible for conversion of superoxide radicals to hydrogen peroxide, is essentially inactive at pH6. Skin pH is generally accepted as being around 1-2 units lower than normal physiological pH (7.3 to 7.4) (Rieger, M (1989). *Cosmetics and Toiletries* 104, 53) and in inflammatory conditions this deviation may be more pronounced. Thus, a significant portion of superoxide anions in the skin will become protonated to form hydroperoxy radicals (HO₂). These combined factors lead to the reduced production of H₂O₂ and hence the anti-inflammatory HOCl.

By the use of a composition according to the present invention, the pH of the affected area is raised to a value close to the pKa of the amino sulfonic acids and thus close to normal physiological pH. This effect, as mentioned above, optimises SOD activity and thus increases HOCl production. In addition, however, the compositions and uses according to the present invention also have a more direct effect on free radicals.

The addition of HEPES or the other zwitterionic amino sulfonic acids listed above to the SOD activity assay has no effect on the rate of reaction. This suggests that these compounds do not scavenge superoxide radicals, on which the stated assay is dependent. However, it is known that HEPES causes a reduction in free radical activity in chemiluminescence-based assays of activated neutrophils, and thus it is proposed that the amino sulfonic acids listed above scavenge free radicals other than superoxide.

Example 6

Hydroperoxyl Scavenging by HEPES

Solid potassium superoxide was added to pure de-ionised water to make a 1.0mM solution. After the vigorous bubbling had stopped, 10ml aliquots were adjusted to pH 2.8 (hydroperoxyl : superoxide ratio 100:1 by equilibrium) with H₂SO₄, and pH 6.8 (hydroperoxyl : superoxide ratio 1:100 by equilibrium) with NaOH.

Nitroso dimethylamine (NDA), which is specifically blocked by hydroperoxyl radicals but not superoxide was added to each aliquot to 10mM and the bleaching followed spectrophotometrically at 440nm. As expected, the aliquot at pH 2.8 bleached NDA whereas that at pH 6.8 did not.

50mM HEPES and 10mM NDA adjusted to pH 2.8 and 6.8 were then added to the pH 2.8 and 6.8 aliquots as above and bleaching followed. 50mM HEPES at pH 2.8 abolished NDA bleaching showing that HEPES scavenged the hydroperoxyl radicals.

In the free radical cascade of ageing and inflammatory processes, the scavenging of

hydroperoxyl radicals by these amino sulfonic acids would cause an increased production of superoxide radicals which, at the optimum pH resulting from the continued presence of the amino sulfonic acid, are readily converted by SOD to H₂O₂ and eventually, by myeloperoxidase, to HOCl.

HEPES and the other zwitterionic amino sulfonic acids can also scavenge hydrogen peroxide under suitable conditions.

Therefore, to summarise the effects of the zwitterionic amino sulfonic acids used in the present invention on antiinflammatory enzymes and free radicals, the presence of the zwitterionic amino sulfonic acids optimises the activity of SOD with respect to pH, thus resulting in greater production of H₂O₂ as a substrate for myeloperoxidase to produce HOCl. In addition, the zwitterionic amino sulfonic acids inhibit conversion of superoxide to hydroperoxyl, both by a pH raising effect and by scavenging of hydroperoxyl radicals, thus providing increased superoxide substrate for SOD. The result is a dramatic increase in the production of antiinflammatory HOCl by means of SOD enhancement.

The compositions, methods and uses of the present invention cause synergistic effects in the abnormal conditions described. The conditions benefit from the normalisation of the environment in which vital enzymes are present and from the enhanced removal of reactive oxygen species from the vicinity of biomolecules. The hydration effect as described above in Example 3 is also an important contributory factor, as is the pH buffering effect, since the decreased need for cells in the affected areas to pump protons from their intracellular compartments will reduce cellular energy expenditure and improve cell integrity, growth, maturation and replication. It is noteworthy that most "skin-care" compositions on the market today are specifically formulated to have a pH of around 5.5. The compositions and uses of the present invention, however, aim to bring the pH of the body surface to which they are applied up to around pH 7.3. In this way, antiinflammatory enzyme activity can be enhanced and cellular energy needs and cellular stress can be reduced.

E) Demonstration of Cell Survival EnhancementExample 7

A mucosal swab was taken from the inner cheek of the human mouth. Cells were incubated at 35°C in Ringer's solution adjusted to pH 5.5 and at pH 7.3 both with and without HEPES at a concentration of 20mM after pH adjustment.

Incubation was over 72 hours and samples were withdrawn at 12 hour intervals. The results showed (by visual microscopy) that at pH 5.5 without HEPES the cell membrane structures became ragged and the cells distorted within the first 24 hours. This did not occur significantly at pH 7.3 without HEPES.

HEPES had little effect at pH5.5 but at pH 7.3 cells in the solution containing HEPES appeared healthier than at pH7.3 without HEPES.

F) Additional EffectsExample 8

Most of the active ingredients currently used in dermatology do not produce normal physiological pH conditions on or in the skin, and therefore when applied topically in commercially available preparations they cause localised skin irritation of varying degrees as a side effect of their use.

The zwitterionic amino sulfonic acids used according to this invention are all general buffers with buffering capacity close to physiological pH. Such use of these zwitterionic amino sulfonic acids, in combination (either in separate formulations, or as a combined formulation) with existing topical products will significantly increase the pH compatibility of the latter with the skin, and thereby decrease the incidence of local irritation reactions. The topical products with which the zwitterionic amino sulfonic acids can be combined include all those in general use in dermatology, particularly those described above. The zwitterionic amino sulfonic acids can also be included in cosmetic compositions to improve the biocompatibility of the latter. The hydrating effect of the zwitterionic amino sulfonic acids may also enhance the penetration and efficacy of other agents.

The zwitterionic amino sulfonic acids for use according to this invention, and in particular HEPES and HEPES sodium therefore provide either a single or a combination of mechanisms by which they are able to correct the underlying aetiology of the abnormal dermatological conditions. Furthermore, these compounds are apparently non-toxic, as demonstrated by industry-standard skin studies in guinea-pigs and rabbits which showed HEPES to be free from hypersensitivity and irritant effects, respectively.

G) Lack of Systemic Absorption

Example 9

Radiolabelled Transdermal Absorption Study

Skin penetration and percutaneous absorption of radioactivity following the topical administration of a single dose of ^{14}C -HEPES (approximately 100mg 5% cream containing 70uCi ^{14}C) was investigated in two groups of six healthy male volunteers. The dose was applied to intact skin in one group and to skin stripped 10 times with scotch tape in the second group. Unabsorbed material was removed after 12 hours and the area of application was then stripped 10 times in order to determine skin penetration. Samples of blood, urine and faeces were collected up to 120 hours after dose application for assessment of total radioactivity.

No radioactivity was detected in any of the plasma or faecal samples, with the exception of one subject in the "stripped skin" group for whom 0.11% of the applied dose was detected in the 48-72 hours faecal sample. Mean urinary excretion of radioactivity in the "intact" and "stripped" groups respectively was 0.07 ± 0.08 (SD) and 0.02 ± 0.22 (SD) percent of the applied dose.

Isolated abnormalities in biochemistry, haematology and urinalysis screens were not considered to be related to ^{14}C -HEPES administration.

In summary, a single topical dose of ^{14}C -HEPES was well tolerated in this study in both "intact" and "stripped" skin groups. Furthermore, in both "intact" and "stripped" skin

groups, there was negligible absorption of radioactivity. This result is in stark contrast to those prior art reports of the activity of zwitterionic amino sulfonic acids in rheumatism and arthritis following topical application to skin.

H) Clinical Studies Example to Clinical Use

Example 10

Clinical Use of HEPES Cream for Psoriasis

28 patients (3 - 56 years of age) with long standing plaque or guttate psoriasis on the body which had proved resistant to all treatments current at the time (including dithranol and pUVA) were treated with either HEPES 0.5 or 1.5% w/w cream. In all cases, a significant or complete clearing of symptoms was seen within 4 weeks and often within 1 week.

Individual Examples

1. 29 year old female with guttate psoriasis of 22 years standing unresponsive to all treatments of the day. Psoriasis affects whole body including the head. Within 2 weeks of use of HEPES cream there was a dramatic improvement in the psoriasis, particularly on the knees.

2. 47 year old male with plaque psoriasis of 18 months standing on legs and feet. Once daily use of HEPES cream lead to a complete clearance of the psoriasis within 7 to 10 days.

In addition 11 patients with scalp psoriasis which had proved resistant to all treatments current at the time (including dithranol and pUVA) were treated with HEPES 2% w/w scalp lotion. In all cases, a significant or complete clearing of symptoms was seen within 6 to 8 weeks.

Further Individual Examples

1. Male with persistent and severe scalp psoriasis which covered the top of his head. After 8 weeks treatment the condition cleared.

2. Female with moderate scalp psoriasis. When assessed after 3 weeks of treatment there was a 40% improvement in the psoriasis. By 6 weeks, the psoriasis had completely cleared.

CLAIMS

1. The use of at least one zwitterionic amino sulfonic acid, having at least one pKa at 25-38°C in the range of 7.3 ± 0.5, in the preparation of a medicament for enhancement of superoxide dismutase activity.
2. Use according to claim 1 wherein the at least one zwitterionic amino sulfonic acid is selected from:

ACES (N-[Carbamoylmethyl]-2-aminoethanesulfonic acid), free acid and all metal salts (pKa=6.8 at 25°C);

PIPES (Piperazine-N,N'-bis[2-ethanesulfonic acid]), free acid and all metal salts (pKa=6.8 at 25°C);

MOPSO (3-[N-morpholino]-2-hydroxypropanesulfonic acid), free acid and all metal salts (pKa=6.9 at 25°C);

BIS-TRIS-Propane (1,3-bis[tris(hydroxymethyl)methylamino]propane), free base and all salts (pKa=6.8 at 25°C);

BES (N,N-bis[2-hydroxyethyl]-2-aminoethanesulfonic acid), free acid and all metal salts (pKa=7.1 at 25°C);

MOPS (3-[N-morpholino]propanesulfonic acid), free acid and all metal salts (pKa=7.2 at 25°C);

TES (N-tris[hydroxymethyl]methyl-2-aminoethanesulfonic acid), free acid and all metal salts (pKa=7.4 at 25°C);

HEPES (N-[2-Hydroxyethyl]piperazine-N'-[2-ethanesulfonic acid]), free acid and all metal salts (pKa=7.5 at 25°C);

DIPSO (3-[N,N-bis(2-hydroxyethyl)amino]-2-hydroxypropanesulfonic acid), free acid and all metal salts (pKa=7.6 at 25°C);

MOBS (4-[N-morpholino]butanesulfonic acid), free acid and all metal salts (pKa=7.6 at 25°C);

TAPSO (3-[N-tris(hydroxymethyl)methylamino]-2-hydroxypropanesulfonic acid), free acid and all metal salts (pKa=7.6 at 25°C);

HEPPSO (N-[2-hydroxyethyl]piperazine-N'-[2-hydroxypropanesulfonic acid], free acid and all metal salts (pKa=7.8 at 25°C); and

POPSO (Piperazine-N,N'-bis[2-hydroxypropanesulfonic acid], free acid and all metal salts (pKa=7.8 at 25°C).

3. Use according to claim 1 or claim 2 wherein one zwitterionic amino sulfonic acid is HEPES.
4. Use according to any of claims 1 to 3 wherein the medicament also includes one or more other compounds known to be efficacious in the treatment or prevention of dermatological disorders and/or non-dermatological inflammatory conditions.
5. A method of enhancing the activity of superoxide dismutase in a patient, the method comprising administering to a patient in need of such treatment an effective superoxide dismutase activity enhancing amount of a composition comprising at least one zwitterionic amino sulfonic acid having at least one pKa at 25-38°C in the range of 7.3 ± 0.5 .
6. A method according to claim 5 wherein the at least one zwitterionic amino sulfonic acid is selected from:

ACES (N-[Carbamoylmethyl]-2-aminoethanesulfonic acid), free acid and all metal salts (pKa=6.8 at 25°C);

PIPES (Piperazine-N,N'-bis[2-ethanesulfonic acid]), free acid and all metal salts (pKa=6.8 at 25°C);

MOPSO (3-[N-morpholino]-2-hydroxypropanesulfonic acid), free acid and all metal salts (pKa=6.9 at 25°C);

BIS-TRIS-Propane (1,3-bis[tris(hydroxymethyl)methylamino]propane), free base and all salts (pKa=6.8 at 25°C);

BES (N,N-bis[2-hydroxyethyl]-2-aminoethanesulfonic acid), free acid and all metal salts (pKa=7.1 at 25°C);

MOPS (3-[N-morpholino]propanesulfonic acid), free acid and all metal salts (pKa=7.2 at 25°C);

TES (N-tris[hydroxymethyl]methyl-2-aminoethanesulfonic acid), free acid and all metal salts (pKa=7.4 at 25°C);

HEPES (N-[2-Hydroxyethyl]piperazine-N'-[2-ethanesulfonic acid]), free acid and all metal salts (pKa=7.5 at 25°C);

DIPSO (3-[N,N-bis(2-hydroxyethyl)amino-2-hydroxy-propanesulfonic acid), free acid and all metal salts (pKa=7.6 at 25°C);

MOBS (4-[N-morpholino]butanesulfonic acid), free acid and all metal salts (pKa=7.6 at 25°C);

TAPSO (3-[N-tris(hydroxymethyl)methylamino]-2-hydroxypropanesulfonic acid), free acid and all metal salts (pKa=7.6 at 25°C);

HEPPSO (N-[2-hydroxyethyl]piperazine-N'-[2-hydroxypropanesulfonic acid), free acid and all metal salts (pKa=7.8 at 25°C); and

POPSO (Piperazine-N,N'-bis[2-hydroxypropanesulfonic acid), free acid and all metal salts (pKa=7.8 at 25°C).

7. A method according to claim 5 or claim 6 wherein one zwitterionic amino sulfonic acid is HEPES.
8. A method according to any of claims 5 to 7 wherein the composition also includes one or more other compounds known to be efficacious in the treatment or prevention of dermatological disorders and/or non-dermatological inflammatory conditions.
9. A moisturiser comprising at least one zwitterionic amino sulfonic acid having at least one pKa in the range 7.3 ± 0.5 at 25-38°C, the moisturiser not containing urea.
10. A moisturiser according to claim 9 also including one or more other active ingredients known to be efficacious in the treatment or prevention of photo and non-photoageing of the skin, iatrogenic skin dryness, mucosal membrane dryness (iatrogenic or non-iatrogenic), skin dryness associated with all forms of psoriasis, skin dryness associated with both photo and non-photo ageing of skin, skin dryness in all forms of dermatitis, skin dryness in all forms of eczema, and skin dryness in all forms of ichthyosis.
11. A moisturiser according to claim 9 or claim 10 also including inert, pharmaceutically acceptable excipients appropriate for the preparation of formulations selected from ointments, creams, injectables, lotions, foams and dressings.

12. A moisturiser according to any of claims 9 to 11 in which at least one zwitterionic amino sulfonic acid is selected from:

ACES (N-[Carbamoylmethyl]-2-aminoethanesulfonic acid), free acid and all metal salts (pKa=6.8 at 25°C);

PIPES (Piperazine-N,N'-bis[2-ethanesulfonic acid]), free acid and all metal salts (pKa=6.8 at 25°C);

MOPSO (3-[N-morpholino]-2-hydroxypropanesulfonic acid), free acid and all metal salts (pKa=6.9 at 25°C);

BIS-TRIS-Propane (1,3-bis[tris(hydroxymethyl)methylamino]propane), free base and all salts (pKa=6.8 at 25°C);

BES (N,N-bis[2-hydroxyethyl]-2-aminoethanesulfonic acid), free acid and all metal salts (pKa=7.1 at 25°C);

MOPS (3-[N-morpholino]propanesulfonic acid), free acid and all metal salts (pKa=7.2 at 25°C);

TES (N-tris[hydroxymethyl]methyl-2-aminoethanesulfonic acid), free acid and all metal salts (pKa=7.4 at 25°C);

HEPES (N-[2-Hydroxyethyl]piperazine-N'-[2-ethanesulfonic acid]), free acid and all metal salts (pKa=7.5 at 25°C);

DIPSO (3-[N,N-bis(2-hydroxyethyl)amino]-2-hydroxy-propanesulfonic acid), free acid and all metal salts (pKa=7.6 at 25°C);

MOBS (4-[N-morpholino]butanesulfonic acid), free acid and all metal salts (pKa=7.6 at 25°C);

TAPSO (3-[N-tris(hydroxymethyl)methylamino]-2-hydroxypropanesulfonic acid), free acid and all metal salts (pKa=7.6 at 25°C);

HEPPSO (N-[2-hydroxyethyl]piperazine-N'-[2-hydroxypropanesulfonic acid), free acid and all metal salts (pKa=7.8 at 25°C); and

POPSO (Piperazine-N,N'-bis[2-hydroxypropanesulfonic acid), free acid and all metal salts (pKa=7.8 at 25°C).

13. A moisturiser according to any of claims 9 to 12 in which one zwitterionic amino sulfonic acid is HEPES.
14. A composition comprising at least one zwitterionic amino sulfonic acid having at least one pKa at 25-38°C in the range of 7.3 ± 0.5 , in combination with one or more agents of known efficacy in the treatment or prevention of dermatological disorders and/or non-dermatological inflammatory conditions, for use in therapy by co-administration or by sequential administration, the composition not containing urea.
15. The use of at least one zwitterionic amino sulfonic acid, having at least one pKa at 25-38°C in the range 7.3 ± 0.5 , and at least one other compound known to be efficacious in the treatment or prevention of dermatological disorders and/or non-dermatological inflammatory conditions in the preparation of a medicament for the treatment of dermatological disorders and/or non-dermatological inflammatory conditions by co-administration or by sequential administration, provided that the medicament does not contain urea.
16. Use according to claim 15 wherein the medicament includes one or more active compounds known to be of use in the prevention or treatment of inflammatory bowel disease, rheumatoid arthritis, asthma, chronic obstructive pulmonary disease

or gastroduodenal inflammation and ulceration.

17. The use of at least one zwitterionic amino sulfonic acid, having at least one pKa at 25-38°C in the range of 7.3 ± 0.5, in the preparation of a medicament for the treatment or prevention of photo and non-photoageing of the skin, iatrogenic skin dryness, mucosal membrane dryness (iatrogenic or non-iatrogenic), skin dryness associated with all forms of psoriasis, skin dryness associated with both photo and non-photo ageing of skin, skin dryness in all forms of dermatitis, skin dryness in all forms of eczema, and skin dryness in all forms of ichthyosis, provided that the medicament does not contain urea.
18. Use according to claim 17 wherein the dermatological disorder is selected from photo and non-photoageing of the skin and mucosal membrane dryness.
19. Use according to claim 17 or claim 18 wherein the at least one zwitterionic amino sulfonic acid is selected from:

ACES (N-[Carbamoylmethyl]-2-aminoethanesulfonic acid), free acid and all metal salts (pKa=6.8 at 25°C);

PIPES (Piperazine-N,N'-bis[2-ethanesulfonic acid]), free acid and all metal salts (pKa=6.8 at 25°C);

MOPSO (3-[N-morpholino]-2-hydroxypropanesulfonic acid), free acid and all metal salts (pKa=6.9 at 25°C);

BIS-TRIS-Propane (1,3-bis[tris(hydroxymethyl)methylamino]propane), free base and all salts (pKa=6.8 at 25°C);

BES (N,N-bis[2-hydroxyethyl]-2-aminoethanesulfonic acid), free acid and all metal salts (pKa=7.1 at 25°C);

MOPS (3-[N-morpholino]propanesulfonic acid), free acid and all metal salts (pKa=7.2 at 25°C);

TES (N-tris[hydroxymethyl]methyl-2-aminoethanesulfonic acid), free acid and all metal salts (pKa=7.4 at 25°C);

HEPES (N-[2-Hydroxyethyl]piperazine-N'-[2-ethanesulfonic acid]), free acid and all metal salts (pKa=7.5 at 25°C);

DIPSO (3-[N,N-bis(2-hydroxyethyl)amino-2-hydroxy-propanesulfonic acid), free acid and all metal salts (pKa=7.6 at 25°C);

MOBS (4-[N-morpholino]butanesulfonic acid), free acid and all metal salts (pKa=7.6 at 25°C);

TAPSO (3-[N-tris(hydroxymethyl)methylamino]-2-hydroxypropanesulfonic acid), free acid and all metal salts (pKa=7.6 at 25°C);

HEPPSO (N-[2-hydroxyethyl]piperazine-N'-[2-hydroxypropanesulfonic acid), free acid and all metal salts (pKa=7.8 at 25°C); and

POPSO (Piperazine-N,N'-bis[2-hydroxypropanesulfonic acid), free acid and all metal salts (pKa=7.8 at 25°C).

20. Use according to any of claims 17 to 19 wherein one zwitterionic amino sulfonic acid is HEPES.

21. Use according to any of claims 17 to 20 wherein the medicament also includes one or more other active compounds known to be of use in the prevention or treatment of photo and non-photoageing of the skin, any form of ichthyosis, any form of dermatitis, any form of eczema, any form of psoriasis, skin dryness associated with photo and non-photo ageing of skin, skin dryness associated with all forms of

psoriasis, iatrogenic skin dryness or mucosal membrane dryness (iatrogenic or non-iatrogenic).

22. The use of at least one zwitterionic amino sulfonic acid, having at least one pKa at 25-38°C in the range 7.3 ± 0.5, in the preparation of a medicament for moisturisation of the skin and/or mucosal membranes, provided that the medicament does not contain urea.
23. Use according to claim 22 wherein the at least one zwitterionic amino sulfonic acid is selected from:

ACES (N-[Carbamoylmethyl]-2-aminoethanesulfonic acid), free acid and all metal salts (pKa=6.8 at 25°C);

PIPES (Piperazine-N,N'-bis[2-ethanesulfonic acid]), free acid and all metal salts (pKa=6.8 at 25°C);

MOPSO (3-[N-morpholino]-2-hydroxypropanesulfonic acid), free acid and all metal salts (pKa=6.9 at 25°C);

BIS-TRIS-Propane (1,3-bis[tris(hydroxymethyl)methylamino]propane), free base and all salts (pKa=6.8 at 25°C);

BES (N,N-bis[2-hydroxyethyl]-2-aminoethanesulfonic acid), free acid and all metal salts (pKa=7.1 at 25°C);

MOPS (3-[N-morpholino]propanesulfonic acid), free acid and all metal salts (pKa=7.2 at 25°C);

TES (N-tris[hydroxymethyl]methyl-2-aminoethanesulfonic acid), free acid and all metal salts (pKa=7.4 at 25°C);

HEPES (N-[2-Hydroxyethyl]piperazine-N'-[2-ethanesulfonic acid]), free acid and all metal salts (pKa=7.5 at 25°C);

DIPSO (3-[N,N-bis(2-hydroxyethyl)amino-2-hydroxy-propanesulfonic acid), free acid and all metal salts (pKa=7.6 at 25°C);

MOBS (4-[N-morpholino]butanesulfonic acid), free acid and all metal salts (pKa=7.6 at 25°C);

TAPSO (3-[N-tris(hydroxymethyl)methylamino]-2-hydroxypropanesulfonic acid), free acid and all metal salts (pKa=7.6 at 25°C);

HEPPSO (N-[2-hydroxyethyl]piperazine-N'-[2-hydroxypropanesulfonic acid), free acid and all metal salts (pKa=7.8 at 25°C); and

POPSO (Piperazine-N,N'-bis[2-hydroxypropanesulfonic acid), free acid and all metal salts (pKa=7.8 at 25°C).

24. Use according to claim 22 or 23 wherein one zwitterionic amino sulfonic acid is HEPES.
25. Use according to any of claims 22 to 24 wherein the medicament also includes one or more other active compounds known to be of use in the prevention or treatment of photo and non-photoageing of the skin, any form of ichthyosis, any form of dermatitis, any form of eczema, any form of psoriasis, skin dryness associated with photo and non-photo ageing of skin, skin dryness associated with all forms of psoriasis, iatrogenic skin dryness or mucosal membrane dryness (iatrogenic or non-iatrogenic).
26. A method of cosmetically improving the appearance of the skin, the method comprising the application to the skin of a composition comprising, as an active ingredient, at least one zwitterionic amino sulfonic acid having at least one pKa at

25-38°C in the range 7.3 ± 0.5, provided that the composition does not contain urea.

27. A method according to claim 26 wherein the at least one zwitterionic amino sulfonic acid is selected from:

ACES (N-[Carbamoylmethyl]-2-aminoethanesulfonic acid), free acid and all metal salts (pKa=6.8 at 25°C);

PIPES (Piperazine-N,N'-bis[2-ethanesulfonic acid]), free acid and all metal salts (pKa=6.8 at 25°C);

MOPSO (3-[N-morpholino]-2-hydroxypropanesulfonic acid), free acid and all metal salts (pKa=6.9 at 25°C);

BIS-TRIS-Propane (1,3-bis[tris(hydroxymethyl)methylamino]propane), free base and all salts (pKa=6.8 at 25°C);

BES (N,N-bis[2-hydroxyethyl]-2-aminoethanesulfonic acid), free acid and all metal salts (pKa=7.1 at 25°C);

MOPS (3-[N-morpholino]propanesulfonic acid), free acid and all metal salts (pKa=7.2 at 25°C);

TES (N-tris[hydroxymethyl]methyl-2-aminoethanesulfonic acid), free acid and all metal salts (pKa=7.4 at 25°C);

HEPES (N-[2-Hydroxyethyl]piperazine-N'-[2-ethanesulfonic acid]), free acid and all metal salts (pKa=7.5 at 25°C);

DIPSO (3-[N,N-bis(2-hydroxyethyl)amino]-2-hydroxy-propanesulfonic acid), free acid and all metal salts (pKa=7.6 at 25°C);

MOBS (4-[N-morpholino]butanesulfonic acid), free acid and all metal salts (pKa=7.6 at 25°C);

TAPSO (3-[N-tris(hydroxymethyl)methylamino]-2-hydroxypropanesulfonic acid), free acid and all metal salts (pKa=7.6 at 25°C);

HEPPSO (N-[2-hydroxyethyl]piperazine-N'-[2-hydroxypropanesulfonic acid), free acid and all metal salts (pKa=7.8 at 25°C); and

POPSO (Piperazine-N,N'-bis[2-hydroxypropanesulfonic acid), free acid and all metal salts (pKa=7.8 at 25°C).

28. A method according to claim 26 or claim 27 wherein one zwitterionic amino sulfonic acid is HEPES.
29. A method according to any of claims 26 to 28 wherein the cosmetic composition also includes one or more agents known to be efficacious in the prevention or treatment of photo and non-photoageing of the skin, any form of ichthyosis, any form of dermatitis, any form of eczema, any form of psoriasis, skin dryness associated with photo and non-photo ageing of skin, skin dryness associated with all forms of psoriasis, iatrogenic skin dryness and mucosal membrane dryness (iatrogenic or non-iatrogenic).
30. A hydroperoxyl radical and/or hydrogen peroxide scavenging composition comprising at least one zwitterionic amino sulfonic acid having at least one pKa at 25-38°C in the range 7.3 ± 0.5 .
31. A composition according to claim 30 in which the at least one zwitterionic amino sulfonic acid is selected from:

ACES (N-[Carbamoylmethyl]-2-aminoethanesulfonic acid), free acid and all metal salts (pKa=6.8 at 25°C);

PIPES (Piperazine-N,N'-bis[2-ethanesulfonic acid]), free acid and all metal salts (pKa=6.8 at 25°C);

MOPSO (3-[N-morpholino]-2-hydroxypropanesulfonic acid), free acid and all metal salts (pKa=6.9 at 25°C);

BIS-TRIS-Propane (1,3-bis[tris(hydroxymethyl)methylamino]propane), free base and all salts (pKa=6.8 at 25°C);

BES (N,N-bis[2-hydroxyethyl]-2-aminoethanesulfonic acid), free acid and all metal salts (pKa=7.1 at 25°C);

MOPS (3-[N-morpholino]propanesulfonic acid), free acid and all metal salts (pKa=7.2 at 25°C);

TES (N-tris[hydroxymethyl]methyl-2-aminoethanesulfonic acid), free acid and all metal salts (pKa=7.4 at 25°C);

HEPES (N-[2-Hydroxyethyl]piperazine-N'-[2-ethanesulfonic acid]), free acid and all metal salts (pKa=7.5 at 25°C);

DIPSO (3-[N,N-bis(2-hydroxyethyl)amino-2-hydroxy-propanesulfonic acid), free acid and all metal salts (pKa=7.6 at 25°C);

MOBS (4-[N-morpholino]butanesulfonic acid), free acid and all metal salts (pKa=7.6 at 25°C);

TAPSO (3-[N-tris(hydroxymethyl)methylamino]-2-hydroxypropanesulfonic acid), free acid and all metal salts (pKa=7.6 at 25°C);

HEPPSO (N-[2-hydroxyethyl]piperazine-N'-[2-hydroxypropanesulfonic acid),

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free acid and all metal salts (pKa=7.8 at 25°C); and

POPSO (Piperazine-N,N'-bis[2-hydroxypropanesulfonic acid]), free acid and all metal salts (pKa=7.8 at 25°C).

32. A composition according to claim 30 or claim 31 in which one zwitterionic amino sulfonic acid is HEPES.

33. A composition according to any of claims 30 to 32 which scavenges extracellular hydroperoxyl radicals and/or hydrogen peroxide.

34. The use of at least one zwitterionic amino sulfonic acid having at least one pKa at 25-38°C in the range 7.3 ± 0.5 in the preparation of a medicament for scavenging hydroperoxyl radicals and/or hydrogen peroxide.

35. Use according to claim 34 wherein the at least one zwitterionic amino sulfonic acid is selected from:

ACES (N-[Carbamoylmethyl]-2-aminoethanesulfonic acid), free acid and all metal salts (pKa=6.8 at 25°C);

PIPES (Piperazine-N,N'-bis[2-ethanesulfonic acid]), free acid and all metal salts (pKa=6.8 at 25°C);

MOPSO (3-[N-morpholino]-2-hydroxypropanesulfonic acid), free acid and all metal salts (pKa=6.9 at 25°C);

BIS-TRIS-Propane (1,3-bis[tris(hydroxymethyl)methylamino]propane), free base and all salts (pKa=6.8 at 25°C);

BES (N,N-bis[2-hydroxyethyl]-2-aminoethanesulfonic acid), free acid and all metal salts (pKa=7.1 at 25°C);

MOPS (3-[N-morpholino]propanesulfonic acid), free acid and all metal salts (pKa=7.2 at 25°C);

TES (N-tris[hydroxymethyl]methyl-2-aminoethanesulfonic acid), free acid and all metal salts (pKa=7.4 at 25°C);

HEPES (N-[2-Hydroxyethyl]piperazine-N'-[2-ethanesulfonic acid]), free acid and all metal salts (pKa=7.5 at 25°C);

DIPSO (3-[N,N-bis(2-hydroxyethyl)amino-2-hydroxy-propanesulfonic acid), free acid and all metal salts (pKa=7.6 at 25°C);

MOBS (4-[N-morpholino]butanesulfonic acid), free acid and all metal salts (pKa=7.6 at 25°C);

TAPSO (3-[N-tris(hydroxymethyl)methylamino]-2-hydroxypropanesulfonic acid), free acid and all metal salts (pKa=7.6 at 25°C);

HEPPSO (N-[2-hydroxyethyl]piperazine-N'-[2-hydroxypropanesulfonic acid), free acid and all metal salts (pKa=7.8 at 25°C); and

POPSO (Piperazine-N,N'-bis[2-hydroxypropanesulfonic acid), free acid and all metal salts (pKa=7.8 at 25°C).

36. Use according to claim 34 or claim 35 wherein one zwitterionic amino sulfonic acid is HEPES.
37. Use according to any of claims 34 to 36 wherein the hydroperoxyl radicals and/or hydrogen peroxide are extracellular.

38. A method of scavenging hydroperoxyl radicals and/or hydrogen peroxide in a patient, the method comprising administering to a patient in need of such treatment an effective scavenging amount of a composition comprising at least one zwitterionic amino sulfonic acid having at least one pKa at 25-38°C in the range 7.3 ± 0.5.

39. A method according to claim 38 wherein the at least one zwitterionic amino sulfonic acid is selected from:

ACES (N-[Carbamoylmethyl]-2-aminoethanesulfonic acid), free acid and all metal salts (pKa=6.8 at 25°C);

PIPES (Piperazine-N,N'-bis[2-ethanesulfonic acid]), free acid and all metal salts (pKa=6.8 at 25°C);

MOPS (3-[N-morpholino]-2-hydroxypropanesulfonic acid), free acid and all metal salts (pKa=6.9 at 25°C);

BIS-TRIS-Propane (1,3-bis[tris(hydroxymethyl)methylamino]propane), free base and all salts (pKa=6.8 at 25°C);

BES (N,N-bis[2-hydroxyethyl]-2-aminoethanesulfonic acid), free acid and all metal salts (pKa=7.1 at 25°C);

MOPS (3-[N-morpholino]propanesulfonic acid), free acid and all metal salts (pKa=7.2 at 25°C);

TES (N-tris[hydroxymethyl]methyl-2-aminoethanesulfonic acid), free acid and all metal salts (pKa=7.4 at 25°C);

HEPES (N-[2-Hydroxyethyl]piperazine-N'-[2-ethanesulfonic acid]), free acid and all metal salts (pKa=7.5 at 25°C);

DIPSO (3-[N,N-bis(2-hydroxyethyl)amino]-2-hydroxypropanesulfonic acid), free acid and all metal salts (pKa=7.6 at 25°C);

MOBS (4-[N-morpholino]butanesulfonic acid), free acid and all metal salts (pKa=7.6 at 25°C);

TAPSO (3-[N-tris(hydroxymethyl)methylamino]-2-hydroxypropanesulfonic acid), free acid and all metal salts (pKa=7.6 at 25°C);

HEPPSO (N-[2-hydroxyethyl]piperazine-N'-[2-hydroxypropanesulfonic acid], free acid and all metal salts (pKa=7.8 at 25°C); and

POPSO (Piperazine-N,N'-bis[2-hydroxypropanesulfonic acid], free acid and all metal salts (pKa=7.8 at 25°C).

40. A method according to claim 38 or claim 39 wherein one zwitterionic amino sulfonic acid is HEPES.

41. A dermal and epidermal cell survival enhancing composition comprising at least one zwitterionic amino sulfonic acid having at least one pKa at 25-38°C in the range 7.3 ± 0.5.

42. A dermal and epidermal cell survival enhancing composition according to claim 41 in which the at least one zwitterionic amino sulfonic acid is selected from:

ACES (N-[Carbamoylmethyl]-2-aminoethanesulfonic acid), free acid and all metal salts (pKa=6.8 at 25°C);

PIPES (Piperazine-N,N'-bis[2-ethanesulfonic acid]), free acid and all metal salts (pKa=6.8 at 25°C);

MOPSO (3-[N-morpholino]-2-hydroxypropanesulfonic acid), free acid and all metal salts (pKa=6.9 at 25°C);

BIS-TRIS-Propane (1,3-bis[tris(hydroxymethyl)methylamino]propane), free base and all salts (pKa=6.8 at 25°C);

BES (N,N-bis[2-hydroxyethyl]-2-aminoethanesulfonic acid), free acid and all metal salts (pKa=7.1 at 25°C);

MOPS (3-[N-morpholino]propanesulfonic acid), free acid and all metal salts (pKa=7.2 at 25°C);

TES (N-tris[hydroxymethyl]methyl-2-aminoethanesulfonic acid), free acid and all metal salts (pKa=7.4 at 25°C);

HEPES (N-[2-Hydroxyethyl]piperazine-N'-[2-ethanesulfonic acid]), free acid and all metal salts (pKa=7.5 at 25°C);

DIPSO (3-[N,N-bis(2-hydroxyethyl)amino-2-hydroxy-propanesulfonic acid), free acid and all metal salts (pKa=7.6 at 25°C);

MOBS (4-[N-morpholino]butanesulfonic acid), free acid and all metal salts (pKa=7.6 at 25°C);

TAPSO (3-[N-tris(hydroxymethyl)methylamino]-2-hydroxypropanesulfonic acid), free acid and all metal salts (pKa=7.6 at 25°C);

HEPPSO (N-[2-hydroxyethyl]piperazine-N'-[2-hydroxypropanesulfonic acid), free acid and all metal salts (pKa=7.8 at 25°C); and

POPSO (Piperazine-N,N'-bis[2-hydroxypropanesulfonic acid), free acid and

all metal salts (pKa=7.8 at 25°C).

43. A composition according to claim 41 or claim 42 in which one zwitterionic amino sulfonic acid is HEPES.
44. The use of at least one zwitterionic amino sulfonic acid having at least one pKa at 25-38°C in the range 7.3 ± 0.5 in the preparation of a medicament for improving epidermal cell integrity and normalising dermal survival, growth, maturation and replication.
45. Use according to claim 44 wherein the at least one zwitterionic amino sulfonic acid is selected from:

ACES (N-[Carbamoylmethyl]-2-aminoethanesulfonic acid), free acid and all metal salts (pKa=6.8 at 25°C);

PIPES (Piperazine-N,N'-bis[2-ethanesulfonic acid]), free acid and all metal salts (pKa=6.8 at 25°C);

MOPSO (3-[N-morpholino]-2-hydroxypropanesulfonic acid), free acid and all metal salts (pKa=6.9 at 25°C);

BIS-TRIS-Propane (1,3-bis[tris(hydroxymethyl)methylamino]propane), free base and all salts (pKa=6.8 at 25°C);

BES (N,N-bis[2-hydroxyethyl]-2-aminoethanesulfonic acid), free acid and all metal salts (pKa=7.1 at 25°C);

MOPS (3-[N-morpholino]propanesulfonic acid), free acid and all metal salts (pKa=7.2 at 25°C);

TES (N-tris[hydroxymethyl]methyl-2-aminoethanesulfonic acid), free acid and

all metal salts (pKa=7.4 at 25°C);

HEPES (N-[2-Hydroxyethyl]piperazine-N'-[2-ethanesulfonic acid]), free acid and all metal salts (pKa=7.5 at 25°C);

DIPSO (3-[N,N-bis(2-hydroxyethyl)amino]-2-hydroxy-propanesulfonic acid), free acid and all metal salts (pKa=7.6 at 25°C);

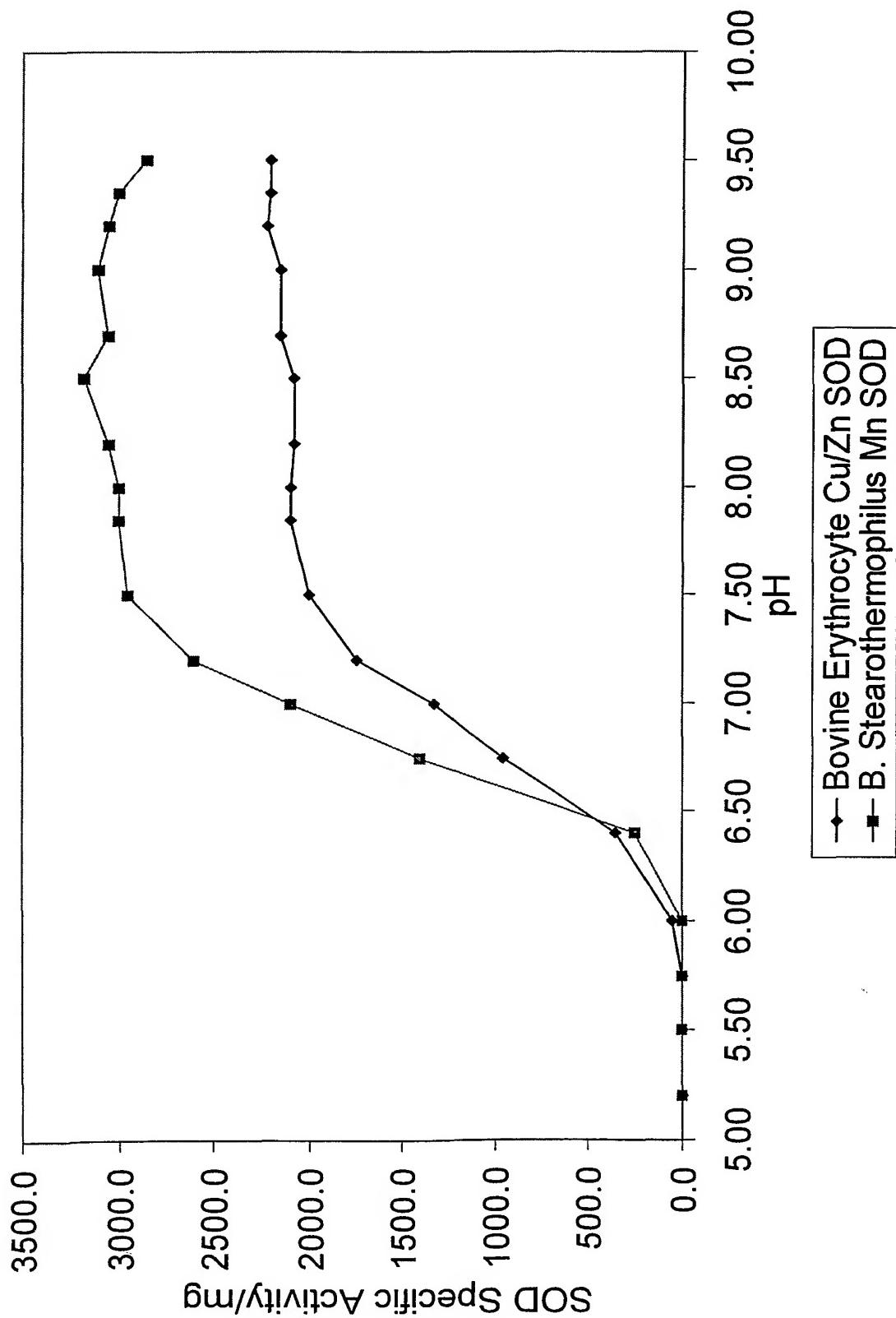
MOBS (4-[N-morpholino]butanesulfonic acid), free acid and all metal salts (pKa=7.6 at 25°C);

TAPSO (3-[N-tris(hydroxymethyl)methylamino]-2-hydroxypropanesulfonic acid), free acid and all metal salts (pKa=7.6 at 25°C);

HEPPSO (N-[2-hydroxyethyl]piperazine-N'-[2-hydroxypropanesulfonic acid], free acid and all metal salts (pKa=7.8 at 25°C); and

POPSO (Piperazine-N,N'-bis[2-hydroxypropanesulfonic acid], free acid and all metal salts (pKa=7.8 at 25°C).

46. Use according to claim 44 or claim 45 wherein one zwitterionic amino sulfonic acid is HEPES.



INTERNATIONAL SEARCH REPORT

PCT/GB 02/01781

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/495 A61K7/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, MEDLINE, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 469 813 A (DERMA SYSTEMS LAB LIMITED) 5 February 1992 (1992-02-05) cited in the application page 3, line 2-31; page 4, line 48-50; example 2-5 ---- WO 88 09657 A (MILLRINE WILLIAM PATRICK) 15 December 1988 (1988-12-15) page 6, line 2 - page 7, line 18; example 1-4 ---- -/-	1-17, 19-21, 26-46
X		1-3,5-7, 9,10,12, 13,17, 19,20, 30-46

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

° Special categories of cited documents :

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- *P* document published prior to the international filing date but later than the priority date claimed

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Date of the actual completion of the international search

5 September 2002

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17.09.02

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INTERNATIONAL SEARCH REPORT

PCT/GB 02/01781

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 228 239 A (SULLIVAN DONNCHA O) 8 July 1987 (1987-07-08) cited in the application column 1, line 27-43; column 2, line 38-51; column 3, line 11-20 ---	1-3, 5-7, 9-13, 26-43
X	EP 0 761 203 A (OREAL) 12 March 1997 (1997-03-12) page 2, line 49 - page 3, line 29; example 1-3 ---	1, 4, 5, 8-11, 14, 15, 17, 18, 21, 26, 29, 34, 37, 38, 41, 44
E	WO 02 39975 A (BERNARD DOMINIQUE ;GALEY JEAN BAPTISTE (FR); OREAL (FR); SIMONETTI) 23 May 2002 (2002-05-23) page 1, line 5-9; page 4, line 20-28; page 5, line 23 - page 6, line 7; page 8, line 19 - page 10, line 2; page 13, line 18 - page 14, line 30; example 2 ---	1, 2, 4-6, 8-12, 14, 15, 17-19, 21, 26, 27, 29-31, 33-35, 37-39, 41, 42, 44, 45
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INTERNATIONAL SEARCH REPORT

PCT/GB 02/01781

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Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: - because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 5-8, 38-40 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition (Rule 39.1(iv) PCT).
2. Claims Nos.: - because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. Claims Nos.: - because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-8, 34-40, 44-46 are formulated as relating to the therapeutic use of aminosulfonic acids. However, the therapeutic application is defined in terms of a mechanism of action, ie the enhancement of superoxide dismutase (claims 1-8) or the scavenging of hydroperoxyl radicals / hydrogen peroxide (claims 34-40) or the improvement of epidermal cell integrity (claims 44-46). A mechanism of action cannot be considered in itself as a therapeutic application. It represents a discovery which still needs to find a practical application in the form of a defined, real treatment of any pathological condition in order to make a technical contribution to the art (Article 33(4) PCT). Moreover, even if the above claims were read as pertaining to the therapeutic use for the treatment of diseases which are defined in functional terms, ie in terms of the mechanism of action postulated for the compounds of the claims, a lack of clarity (Article 6 PCT) concerning the scope of protection afforded by the claims would arise.

Neither the application on file nor the generally accepted knowledge provide instructions in the form of testable criteria or experimental tests allowing the skilled person to recognise which concrete conditions fall within the functional definition and accordingly within the scope of the claims. Therefore, the disclosure (Article 5 PCT) of the application on file is limited to the pathological conditions specifically identified therein and it is not clear (Article 6 PCT), which further diseases could fall within the functional definition chosen in the claims. Because of this lack of disclosure and of clarity a meaningful search could be performed only for those pathological conditions specifically disclosed in the application on file. Those are the dermatological disorders and the non-dermatological inflammatory conditions defined in the description on file (page 1, paragraph 3 – page 12, paragraph 4; page 30-31, example 10).

Dependent claims 2, 6, 12, 19, 23, 27, 31, 35, 39, 42, 45 relate to BIS-TRIS-Propane which is not an amino sulfonic acid. This contradiction between the dependent claims and the corresponding independent claims produces a lack of clarity (Article 6 PCT) as to the scope of protection conferred by these claims. Therefore, the search has been performed for those parts of claims 2, 6, 12, 19, 23, 27, 31, 35, 39, 42, 45 only which are in accordance with the corresponding independent claims and, hence, do not include BIS-TRIS-Propane.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-8, 14-16, 17(part) - 21(part), 30-46

zwitterionic amino sulfonic acids for therapeutic use as antiinflammatory (radical-scavenging and/or leukotriene-reducing) agents in the treatment of those diseases which are specifically disclosed in the application on file (cf. Box 3)

2. Claims: 9-13, 17(part) - 21(part), 22-29

zwitterionic amino sulfonic acids for cosmetic/therapeutic use as moisturising agents